REMARKS

FORMAL MATTERS

Claims 2-10, 15, 20 and 25-76 are pending after entry of the amendments set forth herein, claim 1 being cancelled herein without prejudice or disclaimer, and claims 11-14, 16-19 and 21-24 having been cancelled previously. Claims 40-51 are withdrawn from current consideration.

Claims 2-10, 15, 20, 25-28, 33, 36, 38-42, 46, 49 and 51 are amended. Support for the amendments is found in the claims as originally filed and throughout the specification.

With respect to claims 2-9, 33, 36, 46, 49 and 51, support for an "antibody or a functional fragment thereof" is found in the specification, e.g., at page 8, lines 27-29. Relevant dependent claims are amended for the purpose of antecedent basis.

Claims 10, 15 and 20 are amended to specify that the antibody comprises light and heavy chain sequences comprising the amino acid sequences set forth in the relevant SEQ ID NOs.

Claim 2 is rewritten in independent form, and claims 25, 26, 28, 38-42, 46, 49 and 51 are amended to depend from claim 2.

New dependent Claims 61-74 are added to further claim whole antibodies. Support for these claims is replete throughout the claims and specification as filed, and can be found in particular at, for example, specification page 13, line 26 to page 14, line 18, (see, e.g., page 13, line 26 and line 32).

New dependent Claims 75 and 76 are added. Support for these new claims is found throughout the specification as well as in original Claim 9.

No new matter is added.

REQUEST FOR INTERVIEW

After review of the present response, but prior his next action on the merits, the Examiner is requested to contact Carol Francis at the number provided below to arrange for an interview of the present application.

ITEM 5: REJECTIONS UNDER §112, 1ST PARAGRAPH (WRITTEN DESCRIPTION)

Claims 10, 15 and 20 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Especially to the extent that the rejections are applied to the amended claims, Applicants respectfully traverse.

A patent specification satisfies the written description requirement when it describes the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 U.S.P.Q.2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991).

The Action alleges that there is insufficient written description with respect to antibodies comprising "at least 95% amino acid sequence identity" to the amino acid sequences set forth in claims 10, 15 and 20. It is alleged that the relevant identifying characteristics (e.g., structure or other physical and/or chemical characteristics) of anti-C5aR antibodies are not set forth in the specification.

Applicants respectfully disagree and submit that claims 10, 15 and 20 are adequately supported by the specification (e.g., for the reasons set forth at pp. 10-12 of Applicants' response dated December 14, 2010). However, in the interest of expediting allowance of the instant application, claims 10, 15 and 20 are amended herein to delete the 95% amino acid sequence identity limitation. Applicants submit that the amendments to claims 10, 15 and 20 render the rejections moot. Withdrawal of the rejections is respectfully requested.

ITEM 6: REJECTIONS UNDER §112, FIRST PARAGRAPH (ENABLEMENT)

Claims 5, 8, 29 and 32 are rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement.

To be an enabling disclosure under § 112, first paragraph, a patent must contain a description that enables one skilled in the art to make and use the claimed invention. That some experimentation is necessary does not constitute a lack of enablement; the amount of experimentation, however, must not be unduly extensive. See *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The Action alleges that the supplemental deposit of antibody 12D4 – which is produced by hybridoma cell line 12D4-N17 and has been assigned accession number 04090801 – is not sufficient for satisfying the enablement requirement, absent a statement from a person in a position to corroborate that the antibody deposited is the antibody specifically identified as 12D4 in the application as filed.

Enclosed herewith is a Statement Corroborating Identity of Biological Material executed on April 12, 2011 by Dr. Peter Whitfeld. In the statement, Dr. Whitfeld declares – *inter alia* – that the supplemental deposit is identical to the antibody described as 12D4 in the specification as filed. Applicants submit that the Statement obviates this rejection. Withdrawal of the rejection is respectfully requested.

ITEM 7: REJECTIONS UNDER §112, 1ST PARAGRAPH (WRITTEN DESCRIPTION/NEW MATTER)

Claims 5, 8, 29 and 32 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

A patent specification satisfies the written description requirement when it describes the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See e.g., *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 U.S.P.Q.2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991).

The Action alleges that the specification as originally filed does not provide support for claims directed to a monoclonal antibody as deposited with ECACC under "accession number 04090801." The Examiner acknowledges that this rejection may be obviated by the filing of a statement from a person in a position to corroborate that the antibody deposited is the antibody specifically identified as 12D4 in the application as filed.

As noted above, a Statement Corroborating Identity of Biological Material executed on April 12, 2011 by Dr. Peter Whitfeld is enclosed herewith. In the statement, Dr. Whitfeld declares – *inter alia* – that the supplemental deposit is identical to the antibody described as 12D4 in the specification as filed. Applicants submit that the Statement obviates this rejection. Withdrawal of the rejection is respectfully requested.

ITEM 8: THE SPECIFICATION

The amendment to the specification filed on November 2, 2009, is objected to under 35 U.S.C. §132 for allegedly introducing new matter into the disclosure. Specifically, the Action alleges that the amendment to the specification stating that "(12D4-N17) was deposited on September 8, 2004 with ECACC under accession number 04090801" is not supported by the original disclosure.

The Examiner acknowledges that this objection may be obviated by the filing of a statement from a person in a position to corroborate that the antibody deposited is the antibody specifically identified as 12D4 in the application as filed. As noted above in Applicants' responses to the rejections at Items 6 and 7 of the Action, a Statement Corroborating Identity of Biological Material executed on April 12, 2011 by Dr. Peter Whitfeld is enclosed herewith. In the statement, Dr. Whitfeld declares – *inter alia* – that the supplemental deposit is identical to the antibody described as 12D4 in the specification as filed. Applicants submit that the Statement obviates the objection to the specification. Withdrawal of the objection is respectfully requested.

ITEM 9: REJECTIONS UNDER §103(A)

Claims 1-9, 25-28 and 33-39 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over USPN 5,480,974 to Morgan et al. (hereinafter "Morgan"), in view of Cain et al. (*Biochemical Pharmacology* (2001) 61: 1571-1579) (hereinafter "Cain"), Crass et al. (*J. Biol. Chem.* (1999) 274: 8367-8370) (hereinafter "Crass"), Oppermann et al. (*J. Immunol.* (1993) 151: 3785-3794) (hereinafter "Oppermann") and Pease et al. (*Eur. J. Immunol.* (1994) 24: 211-215) (hereinafter "Pease"). Applicants respectfully traverse for the reasons set forth below.

According to the post-*KSR* Patent Office promulgated examination guidelines on determination of obviousness, when office personnel reject claims by attempting to combine prior art elements according to allegedly known methods to yield predictable results, the Office must resolve the Graham factual inquiries and articulate:

(1) "a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference;"

(2) "a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely would have performed the same function as it did separately; and"

(3) "a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable." (Federal Register / Vol. 72, No. 195 / Wednesday, October 10, 2007 / Notices at 57529, *citing KSR International Co. v. Teleflex Inc.*, 82 U.S.P.Q. 2d 1385, 1395 (U.S. 2007)).

Thus, the rationale to support a conclusion that a claim would have been obvious is that "all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions," and that "the combination would have yielded nothing more than predictable results to one of ordinary skill in the art at the time of the invention." *Id.*

Applicants submit that the combination of Morgan in view of Cain, Crass, Oppermann and Pease does not render the claimed invention obvious, at least because: (1) the cited references indicate that one of skill would not have reasonably expected that antibodies reactive with the second extracellular loop would be effective for reducing or inhibiting the binding of C5a to C5aR; and (2) the antibodies of the present invention exhibit the unexpected property of being significantly more effective than antibodies reactive with the N-terminus of C5aR in blocking and neutralizing C5a binding to C5aR and chemotaxis of neutrophils and other cells expressing human C5aR.

A Reasonable Expectation of Success was Absent

A reasonable expectation of success is required to support a *prima facie* case of obviousness. See MPEP 2143.02. Applicants submit that the only references in the cited combination that disclose anti-C5aR antibodies – Morgan and Oppermann – clearly indicate that one of skill in the art, prior to Applicants' disclosure, would not have reasonably expected that antibodies reactive with the second extracellular loop would be effective for reducing or inhibiting the binding of C5a to C5aR as recited in the present claims.

Morgan only discloses an antibody that binds to the N-terminal domain of C5aR. Morgan teaches that the N-terminal domain is a particularly desirable target relative to other portions of the receptor due to its hydrophilicity and potential exposure to the surface of the cell

membrane. See Morgan, column 16, lines 12-14. Despite the careful selection of residues 9-29 of C5aR for raising a polyclonal antibody, the resulting antibody was only effective in neutralizing chemotaxis of neutrophils at very high concentrations. Maximum inhibition of neutrophil chemotaxis required 800 μg/ml of the antibody. See Morgan, column 19, line 16. It is worth noting that only 1.5 μg/ml of Applicants' mAb 7F3 antibody was required to completely inhibit chemotaxis of neutrophils. See Figure 5 of the instant application. Upon reviewing Morgan, one of ordinary skill would believe that the N-terminal domain provides the best target for generating an antibody against C5aR, but in the best case scenario, extremely high concentrations of the antibody would be required to inhibit chemotaxis of neutrophils. In view of Morgan, one of ordinary skill would not have believed that an antibody raised against a portion of C5aR other than the N-terminal domain would be effective, *at any concentration*, for reducing or inhibiting C5a binding to C5aR.

Oppermann is similarly deficient as a reference for purposes of supporting a *prima facie* case of obviousness against the claimed invention. Oppermann discloses polyclonal antibodies raised using peptides of various domains of C5aR, including the N-terminal domain and the first, second and third extracellular loops. Results of experiments to assess the ability of these antibodies to inhibit binding of C5a to C5aR are shown in Table IV of Oppermann. Table IV clearly shows that only antibodies reactive with the N-terminal domain were capable of inhibiting C5a binding to C5aR. As established in Applicants' response dated December 14, 2010, Oppermann expressly dismisses the use of anti-C5aR antibodies reactive with a portion of C5aR other than the N-terminal domain for reducing or inhibiting C5a binding. Two such examples include the following:

> As shown in Table IV the pretreatment of PMN with EX1-specific polyclonal antibodies reduces binding of C5aF by 75%. In contrast, antibodies with specificities for the extracellular domains EX2, EX3 and EX4 did not interfere with C5a binding to its receptor. See Oppermann, emphasis added, p. 3790, first paragraph, right hand column (emphasis added).

and

> The preabsorption of C5aR on PMN with polyclonal antibodies against its extracellular domains EX2, EX3 or EX4 did not inhibit C5a

> binding, nor did the preabsorption of receptors with an excess of C5a prevent the binding of these antibodies to cells. The extracellular loops EX2, EX3 or EX4 therefore appear not to contain essential ligand binding sites. In contrast, C5a and anti-EX1 mAb and polyclonal antibodies mutually interfered with their binding to the C5aR. See Oppermann, emphasis added, p. 3792, first full paragraph, right hand column.

From the above, it is clear that not only does Oppermann refute any notion that a reasonable expectation of success existed at the time the instant application was filed, but Oppermann expressly *teaches away* from instant claims 2-9, 25-28 and 33-39, which relate to antibodies reactive with the second extracellular loop of C5aR.

Accordingly, a plain reading of Morgan and Oppermann would steer one of skill away from using an antibody raised against any portion of C5aR other than the N-terminal domain. None of Cain, Crass or Pease provide a teaching that counteracts the teachings of Morgan and Oppermann that the present invention lacked a reasonable expectation of success at the time the present invention was made. Prior to Applicants' disclosure, one of skill simply would not have reasonably expected that an antibody reactive with the second extracellular loop of C5aR would be effective for reducing or inhibiting the binding of C5a to C5aR. For this reason alone, the cited combination fails to render the claimed invention obvious and Applicants respectfully request withdrawal of the rejection.

Applicants' Antibodies Possess Unexpectedly Improved Properties

MPEP §2145 sets out the principles in considering rebuttal arguments by applicants against obviousness, stating in part that: "Rebuttal evidence may also include evidence that the claimed invention yields *unexpectedly improved properties or properties not present in the prior art*." Emphasis added. As set forth below, Applicants submit that the antibodies of the claimed invention exhibit unexpectedly improved properties and properties not present in the prior art.

In light of the state of the art at the time of the instant application, it was unexpected that Applicants' antibodies generated against the second extracellular loop of C5aR would be effective to reduce or inhibit C5a binding. In addition, the antibodies of the claimed invention possess unexpectedly *improved* properties with respect to robust reduction or inhibition of C5a binding compared to the antibodies raised against the N-terminal domain of C5aR, e.g., of Morgan and Oppermann. Moreover, these properties were not present in the prior art, as no

antibody reactive with the second extracellular loop of C5aR had been shown to reduce or inhibit C5a binding.

These unexpected advantages are highlighted, for example, in Figures 2 and 4 of the present application. Figure 2 shows the results of ligand binding assays involving C5a and a range of monoclonal antibodies raised against C5aR. The antibodies 12D4, 6C12 and 7F3 were the only antibodies of this group which bind to the second extracellular loop of C5aR. The monoclonal antibodies 5H11, 5F3, 8D6, 11B9 and 1D12 all bind to the N-terminal loop. The binding site of 10G1 and 10D4 has not been clearly elucidated as yet. Figure 2 shows that all antibodies that bind to the second extracellular loop on average were able to inhibit binding of C5a to C5aR to a greater extent than other antibodies.

Figure 4 of the present application provides results of chemotaxis experiments which further support the unexpected properties of the claimed antibodies. Chemotaxis is a biological activity mediated by C5aR. Chemotaxis occurs when C5a binds to C5aR expressed on leukocytes and facilitates movement of those leukocytes from blood to tissue thereby generating an inflammatory response. The results in Figure 4 show that the antibodies directed against the second extracellular loop (i.e. 12D4, 6C12 and 7F3) exhibited vastly improved inhibition of chemotaxis as compared to antibodies directed against other extracellular loops of C5aR.

The above results were published by Lee et al. (*Nature Biotechnology* (2006) 24(10): 1279-1284; copy enclosed). This paper includes the results presented in Figure 2 of the present application together with results relating to additional anti-C5aR antibodies that were generated after the filing of the present application and which are described in WO 2008/022390. The ability of all of these antibodies to block C5aR was assessed and results are shown in Supplementary Figure 1 and Figure 2b. The results are accurately summarized as follows:

> Of the 24 antibodies tested, most bound to either the N terminus or the second extracellular loop of human C5aR. However, <u>without exception</u>, <u>all antibodies with the most potent C5aR blocking activity bound to the second extracellular loop</u> (Fig. 2b). <u>See</u> Lee et al., emphasis added, page 1280, right column, final paragraph.

The improved blocking capabilities of antibodies against the second extracellular loop were highly unexpected at the time of Applicants' invention – in fact, all of the prior art

documents (including Morgan and most especially Oppermann) promote the N-terminal loop as the vastly preferable region of C5aR against which better target for blocking antibodies.

Finally, WO2009/103113 is a publication related to the present application which describes humanized version of MAb 7F3, one of the antibodies described in the present application which binds to the second extracellular loop of C5aR. These humanized antibodies were shown to bind to the same epitope as 7F3 (see Example 4) and to be effective in blocking chemotaxis of cells expressing C5aR (see figures 16 and 17 and the results presented in Example 5). Accordingly, this publication provides evidence that antibodies which bind to the same epitopes as those described in the present application are also particularly effective in blocking C5aR activity.

<u>Conclusion Regarding Obviousness</u>

The cited references, including the only two that actually disclose antibodies against C5aR (Morgan and Oppermann), clearly indicate that a reasonable expectation that the second extracellular loop-specific antibodies of the present invention could reduce or inhibit C5a binding to C5aR, and in turn vastly inhibit chemotaxis, was completely absent prior to Applicants' disclosure. Moreover, these antibodies exhibit unexpectedly improved properties in their ability to inhibit C5a binding much more efficiently than the N-terminal-specific antibodies which had been considered the "gold standard" prior to Applicants' invention. Finally, these properties were not present in the prior art, as no antibody reactive with the second extracellular loop of C5aR had been shown to reduce or inhibit C5a binding, let alone reduce or inhibit C5a binding to a significantly greater extent that those disclosed, e.g., by Morgan and Oppermann. At least for these reasons, the combination of Morgan in view of Cain, Crass, Oppermann and Pease fails to render the claimed invention obvious. Accordingly, Applicants respectfully request withdrawal of the rejection.

CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number RICE-032.

Respectfully submitted,

BOZICEVIC, FIELD & FRANCIS LLP

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Date: May 27, 2011

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Enclosures:

- Request for Continued Examination;
- Statement Corroborating Identity of Biological Material;
- Lee et al. (*Nature Biotechnology* (2006) 24(10): 1279-1284) including supplementary Figure 1; and
- Information Disclosure Statement.

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